Title

Cardiovascular Screening for a Patient Conceived through Assisted Reproductive Technology

Journal

Proceedings of UCLA Health, 21(1)

Authors

Cheong, Kimberly
Kochar, Minisha

Publication Date

2017-05-31

Proceedings of UCLA Healthcare
-VOLUME 21 (2017)-

CLINICAL VIGNETTE

Cardiovascular Screening for a Patient Conceived through Assisted Reproductive Technology

Kimberly Cheong, M.D. and Minisha Kochar, M.D.

A cardiologist (MK) was recently asked to consult on a 22-year-old patient who was conceived through Assisted Reproductive Technology (ART). Her mother was unable to conceive spontaneously due anatomic abnormalities of her fallopian tubes. The patient had no known medical problems. However, she was concerned that individuals conceived through ART were at increased risk of heart disease relative to the general population and inquired if she needed any preventative screening. This patient's query prompted a review of the available data.

The world's first "test tube baby" Louise Brown was born on July 25, 1978 at Oldham General Hospital in England. Since then, more than 5 million children have been conceived through ART as novel in-vitro fertilization techniques have been developed, medication regimens further refined, costs have decreased, and the process has generally become more culturally accepted by the public.[1] Current statistics indicate that 2% of all births worldwide and 1% of live births in the US at this time are attributable to ART.[2]

Pregnancies conceived by ART are at higher risk for adverse birth outcomes relative to spontaneous conception: these include multiple births, low birth weight, and pre-term delivery.[3,4] ART may also impair placental development and function, thus affecting intrauterine fetal growth.[5-8] Concerns have been raised about the health of the offspring born via ART, including an increased risk of birth defects, cancers, delayed growth, and developmental disorders. As children of ART are getting older there is growing concern about the frequency of age-related disorders including type 2 diabetes and cardiovascular disease.[9-14]

Specifically looking at cardiovascular disease, multiple studies have shown elevated systolic and diastolic blood pressures in children conceived through ART.[15-16] A study by *Celeen et al.* looked at the differences in systolic and diastolic blood pressure in ART-conceived children.[15] In their population of 8 to 18-year olds, there was a significant difference in both systolic (3-4 mm Hg) and diastolic (1-2 mm Hg) blood pressure readings relative to the age and weight-matched controls that were spontaneously conceived.

While these numbers may sound minimal, increased blood pressure is associated with a higher long-term risk of stroke and cardiovascular disease. Lowering the mean systolic blood pressure by 2 mm Hg corresponds to an 8% reduction in the risk of stroke.[17] In the same study by Celeen et al., ART children had a significantly higher sum of skin folds, which correlated to increased body fat and higher glucose levels. Height, weight, and BMI were comparable between the two populations.[15]

With regard to cardiac structure and function, von Arx et al showed increased right ventricular dysfunction in children and adolescents conceived by ART relative to controls.[18] An additional 2012 study showed systemic and pulmonary vascular dysfunction in 7 to 18-year-olds conceived through ART when compared with age-matched controls.[19] As ART-conceived children grow, there is speculation that these individuals may be at higher risk for developing type 2 diabetes and metabolic syndrome.[16,19-22] Studies to date have been small and have measured different parameters. Celeen et al reported that ART may impair fasting blood glucose metabolism, irrespective of early life factors.[15] Sakka et al showed no increase in insulin resistance in ART-conceived children, however, this population had significantly higher triglyceride levels.[16] It is unclear which of these metabolic abnormalities result from the ART versus the hereditary metabolic profile of the parents. Some metabolic illnesses are associated with an inability to conceive, i.e. polycystic ovarian syndrome.

Hormonal abnormalities in ART-conceived children may be due to the high circulating maternal gonadotropins which are used to stimulate oocyte maturation during the ART process. A condition called OHSS (Ovarian Hyperstimulation Syndrome) can occur during the stimulation of ovaries in ART and is associated with supraphysiologic maternal estradiol and progesterone levels. This lasts throughout the first trimester and can lead to intravascular depletion of fluid with oliguria, electrolyte imbalance, and thromboembolic phenomenon in the mother, the effects of which may be transferred to the fetus.[22,23]

Epigenetic changes may also play a role in metabolic functioning of ART-conceived children. Epigenetics is defined as heritable changes in gene expression without alterations in DNA sequence.[24] Epigenetic modifications regulate the spatial

and temporal gene expressions necessary during embryonic, fetal, and post-natal development.[2] There are two recognized instances of epigenetic manipulation during gametogenesis and early pre-implantation. Manipulation of the oocyte or blastocyst during ART may impair this process, the effects of which may persist into or only become manifest during adulthood.[26,27]

Returning to our patient, a thorough history was obtained. She had normal vital signs and a normal physical examination. Based on the literature reviewed, no cardiac functional or structural testing was clinically indicated. I encouraged regular preventive visits with her PCP as well as a healthy lifestyle with exercise and a mindful diet, and follow-up for routine age-related preventative screenings.

REFERENCES

1. **Ferraretti AP, Goossens V, Kupka M, Bhattacharya S, de Mouzon J, Castilla JA, Erb K, Korsak V, Nyboe Andersen A; European IVF-Monitoring (EIM) Consortium for the European Society of Human Reproduction and Embryology (ESHRE).** Assisted reproductive technology in Europe, 2009: results generated from European registers by ESHRE. *Hum Reprod*. 2013 Sep;28(9):2318-31. doi:10.1093/humrep/det278. Epub 2013 Jul 9. PubMed PMID: 23842560.
2. **Wright VC, Chang J, Jeng G, Macaluso M; Centers for Disease Control and Prevention (CDC).** Assisted reproductive technology surveillance--United States, 2005. *MMWR Surveill Summ*. 2008 Jun 20;57(5):1-23. Erratum in: *MMWR Surveill Summ*. 2009 Mar 6;58(8):203-4. *MMWR Surveill Summ*. 2008 Oct 10;57(40):1105. PubMed PMID:18566567.
3. **Hart R, Norman RJ.** The longer-term health outcomes for children born as a result of IVF treatment: Part I--General health outcomes. *Hum Reprod Update*. 2013 May-Jun;19(3):232-43. doi: 10.1093/humupd/dms062. Epub 2013 Feb 28. Review. PubMed PMID: 23449642.
4. **Bergh T, Ericson A, Hillensjö T, Nygren KG, Wennerholm UB.** Deliveries and children born after in-vitro fertilisation in Sweden 1982-95: a retrospective cohort study. *Lancet*. 1999 Nov 6;354(9190):1579-85. PubMed PMID: 10560671.
5. **Chen S, Sun FZ, Huang X, Wang X, Tang N, Zhu B, Li B.** Assisted reproduction causes placental maldevelopment and dysfunction linked to reduced fetal weight in mice. *Sci Rep*. 2015 Jun 18;5:10596. doi: 10.1038/srep10596. PubMed PMID:26085229; PubMed Central PMCID: PMC4471727.
6. **Li B, Chen S, Tang N, Xiao X, Huang J, Jiang F, Huang X, Sun F, Wang X.** Assisted Reproduction Causes Reduced Fetal Growth Associated with Downregulation of Paternally Expressed Imprinted Genes That Enhance Fetal Growth in Mice. *Biol Reprod*. 2016 Feb;94(2):45. doi: 10.1095/biolreprod.115.136051. Epub 2016 Jan 13. PubMed PMID: 26764349.
7. **de Waal E, Vrooman LA, Fischer E, Ord T, Mainigi MA, Coutifaris C, Schultz RM, Bartolomei MS.** The cumulative effect of assisted reproduction procedures on placental development and epigenetic perturbations in a mouse model. *Hum Mol Genet*. 2015 Dec 15;24(24):6975-85. doi: 10.1093/hmg/ddv400. Epub 2015 Sep 23. PubMed PMID: 26401051; PubMed Central PMCID: PMC4654053.
8. **Bloise E, Lin W, Liu X, Simbulan R, Kolahi KS, Petraglia F, Maltepe E, Donjacour A, Rinaudo P.** Impaired placental nutrient transport in mice generated by in vitro fertilization. *Endocrinology*. 2012 Jul;153(7):3457-67. doi:10.1210/en.2011-1921. Epub 2012 May 4. PubMed PMID: 22562173; PubMed Central PMCID: PMC3380310.
9. **Sutcliffe AG, Ludwig M.** Outcome of assisted reproduction. *Lancet*. 2007 Jul 28;370(9584):351-9. Review. PubMed PMID: 17662884.
10. **Allen VM, Wilson RD, Cheung A; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC); Reproductive Endocrinology Infertility Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC).** Pregnancy outcomes after assisted reproductive technology. *J Obstet Gynaecol Can*. 2006 Mar;28(3):220-50. English, French. PubMed PMID:16650361.
11. **Ludwig AK, Sutcliffe AG, Diedrich K, Ludwig M.** Post-neonatal health and development of children born after assisted reproduction: a systematic review of controlled studies. *Eur J Obstet Gynecol Reprod Biol*. 2006 Jul;127(1):3-25. Epub 2006 Apr 18. Review. PubMed PMID: 16621225.
12. **Chung K, Coutifaris C, Chalian R, Lin K, Ratcliffe SJ, Castelbaum AJ, Freedman MF, Barnhart KT.** Factors influencing adverse perinatal outcomes in pregnancies achieved through use of in vitro fertilization. *Fertil Steril*. 2006 Dec;86(6):1634-41. Epub 2006 Oct 30. PubMed PMID: 17074345.
13. **Wisborg K, Ingerslev HJ, Henriksen TB.** IVF and stillbirth: a prospective follow-up study. *Hum Reprod*. 2010 May;25(5):1312-6. doi: 10.1093/humrep/deq023. Epub 2010 Feb 23. PubMed PMID: 20179321.
14. **Basatemur E, Sutcliffe A.** Follow-up of children born after ART. *Placenta*. 2008 Oct;29 Suppl B:135-40. doi: 10.1016/j.placenta.2008.08.013. Review. PubMed PMID: 18790325.
15. **Ceelen M, van Weissenbruch MM, Vermeiden JP, van Leeuwen FE, Delemarre-van de Waal HA.** Cardiometabolic differences in children born after in vitro fertilization: follow-up study. *J Clin Endocrinol Metab*. 2008 May;93(5):1682-8. doi: 10.1210/jc.2007-2432. Epub 2008 Feb 19. PubMed PMID: 18285409.
16. **Sakka SD, Loutradis D, Kanaka-Gantenbein C, Margeli A, Papastamataki M, Papassotiriou I, Chrousos GP.** Absence of insulin resistance and low-grade inflammation despite early metabolic syndrome manifestations in children born after in vitro fertilization. *Fertil Steril*. 2010 Oct;94(5):1693-9. doi:10.1016/j.fertnstert.2009.09.049. Epub 2010 Jan 4. PubMed PMID: 20045517.
17. **MacMahon S.** Blood pressure and the prevention of stroke. *J Hypertens Suppl*. 1996 Dec;14(6):S39-46. Review. PubMed PMID: 9023715.
18. **von Arx R, Allemann Y, Sartori C, Rexhaj E, Cerny D, de Marchi SF, Soria R, Germond M, Scherrer U,**

Rimoldi SF. Right ventricular dysfunction in children and adolescents conceived by assisted reproductive technologies. *J Appl Physiol* (1985). 2015 May 15;118(10):1200-6. doi: 10.1152/japplphysiol.00533.2014. Epub 2015 Apr 2. PubMed PMID: 25979934.

19. **Scherrer U, Rimoldi SF, Rexhaj E, Stuber T, Duplain H, Garcin S, de Marchi SF, Nicod P, Germond M, Allemann Y, Sartori C.** Systemic and pulmonary vascular dysfunction in children conceived by assisted reproductive technologies. *Circulation*. 2012 Apr 17;125(15):1890-6. doi: 10.1161/CIRCULATIONAHA.111.071183. Epub 2012 Mar 20. PubMed PMID: 22434595.
20. **Ceelen M, van Weissenbruch MM, Roos JC, Vermeiden JP, van Leeuwen FE, Delemarre-van de Waal HA.** Body composition in children and adolescents born after in vitro fertilization or spontaneous conception. *J Clin Endocrinol Metab*. 2007 Sep;92(9):3417-23. Epub 2007 Jun 26. PubMed PMID: 17595253.
21. **Chen M, Wu L, Zhao J, Wu F, Davies MJ, Wittert GA, Norman RJ, Robker RL, Heilbronn LK.** Altered glucose metabolism in mouse and humans conceived by IVF. *Diabetes*. 2014 Oct;63(10):3189-98. doi: 10.2337/db14-0103. Epub 2014 Apr 23. PubMed PMID: 24760136.
22. **Hu XL, Feng C, Lin XH, Zhong ZX, Zhu YM, Lv PP, Lv M, Meng Y, Zhang D, Lu XE, Jin F, Sheng JZ, Xu J, Huang HF.** High maternal serum estradiol environment in the first trimester is associated with the increased risk of small-for-gestational-age birth. *J Clin Endocrinol Metab*. 2014 Jun;99(6):2217-24. doi: 10.1210/jc.2013-3362. Epub 2014 Feb 28. PubMed PMID: 24606075.
23. **Nastri CO, Ferriani RA, Rocha IA, Martins WP.** Ovarian hyperstimulation syndrome: pathophysiology and prevention. J Assist Reprod Genet. 2010 Feb;27(2-3):121-8. doi: 10.1007/s10815-010-9387-6. Epub 2010 Feb 6. Review. PubMed PMID: 20140640; PubMed Central PMCID: PMC2842872.
24. **Waddington CH.** The epigenotype. 1942. *Int J Epidemiol*. 2012 Feb;41(1):10-3. doi: 10.1093/ije/dyr184. Epub 2011 Dec 20. PubMed PMID: 22186258.
25. **Le Bouc Y, Rossignol S, Azzi S, Steunou V, Netchine I, Gicquel C.** Epigenetics, genomic imprinting and assisted reproductive technology. *Ann Endocrinol* (Paris). 2010 May;71(3):237-8. doi: 10.1016/j.ando.2010.02.004. Epub 2010 Apr 2. PubMed PMID: 20362968.
26. **Laprise SL.** Implications of epigenetics and genomic imprinting in assisted reproductive technologies. *Mol Reprod Dev*. 2009 Nov;76(11):1006-18. doi: 10.1002/mrd.21058. Review. PubMed PMID: 19484754.
27. **Reik W, Walter J.** Genomic imprinting: parental influence on the genome. *Nat Rev Genet*. 2001 Jan;2(1):21-32. Review. PubMed PMID: 11253064.

Submitted May 31, 2017